Preliminary Results of a Phase 1/2 Clinical Study of Zinc Finger Nuclease-Mediated Editing of BCL11A in Autologous Hematopoietic Stem Cells for Transfusion-Dependent Beta Thalassemia

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Public Summary:

Scientific Abstract:
Introduction: Persistently high fetal hemoglobin (HbF) expression can ameliorate severe transfusion-dependent beta thalassemia (TDT). BCL11A, a master regulator of the fetal-to-adult hemoglobin switch, is a rational gene-editing target in beta globinopathies. In pre-clinical studies with human hematopoietic stem cells (HSC), zinc finger nuclease (ZFN)-mediated disruption of the GATA-binding region of the intronic erythroid-specific enhancer (BCL11A ESE) increased endogenous HbF production in erythroid cells while allowing healthy, multi-lineage hematopoiesis. Though allogeneic hematopoietic stem cell transplantation (HSCT) can be curative in TDT, its application is partly limited by donor availability. Autologous transplantation using ex vivo gene-modified HSCs (HSCGT) can circumvent this, and lentiviral vector-mediated beta globin gene addition studies have shown efficacy in TDT. However, the long-term safety of random lentiviral genomic integration in HSCs is uncertain. ST-400 is an investigational cell therapy comprised of autologous CD34+ cells that have undergone high-precision, ZFN-mediated ex vivo editing at BCL11A ESE. The aim of this study is to induce HbF expression in edited erythroid cells. We hypothesized that HSCGT with ST-400 is safe and effective in TDT.